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1634

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Jonathan GERSHONI et al.

Art Unit: 1634

Application No.: 09/297,668 Conf. No. 1117

Examiner: Betty J. Forman

Filed: May 6, 1999

Washington, D.C.

For: DETERMINATION AND CONTROL OF BIMOLECULAR INTERACTIONS

Atty.'s Docket: GERSHONI=5

Date: October 2, 2003

THE COMMISSIONER OF PATENTS
2011 South Clark Place, Mail Stop
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

Transmitted herewith is a [ ] Amendment [XX] Response _____
in the above-identified application.

[XX] Small Entity Status: Applicant(s) claim small entity status. See 37 C.F.R. §1.27.

[ ] No additional fee is required.

[XX] The fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA EQUALS	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
TOTAL	*	MINUS	**	0	x 9	$		x 18	$
INDEP.	*	MINUS	***	0	x 43	$		x 86	$
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+ 145	$		+ 290	$
					ADDITIONAL FEE TOTAL	$	OR	TOTAL	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[XX] Conditional Petition for Extension of Time
If any extension of time for a response is required, applicant requests that this be considered a petition therefor.

[XX] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity Response Filed Within			Other Than Small Entity Response Filed Within		
[XX]	First	- $ 55.00	[ ]	First	- $ 110.00
[ ]	Second	- $ 210.00	[ ]	Second	- $ 420.00
[ ]	Third	- $ 475.00	[ ]	Third	- $ 950.00
[ ]	Fourth	- $ 740.00	[ ]	Fourth	- $ 1480.00
Month After Time Period Set			Month After Time Period Set		

[ ] Less fees ($_____) already paid for ___ month(s) extension of time on _____.

[ ] Please charge my Deposit Account No. 02-4035 in the amount of $_____.

[XX] Credit Card Payment Form, PTO-2038, is attached, authorizing payment in the amount of $55.00.

[ ] A check in the amount of $_____ is attached (check no.).

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR §1.16 and all patent processing fees under 37 CFR §1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR §1.18.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: GERSHONI 5

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REPONSE

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, Mail Stop
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

The present communication is responsive to the official action of June 2, 2003. Claims 144-182 presently appear in this case. Claims 157, 158, 171-176, 178 and 180-182 have been withdrawn from consideration. No claims have been allowed. The official action of June 2, 2003, has now been carefully studied. Reconsideration and allowance are respectfully urged.

Briefly, the present invention relates to a method for identifying continuous peptides which simulate a discontinuous epitope of a single biological unit, i.e., which interact with a ligand which interacts with a discontinuous epitope of a single biological unit. The single biological unit may be a protein or a complex of proteins. It may also

be a DNA or RNA unit. The DNA, which may be the DNA that comprises the biological unit or that corresponds to the RNA of the biological unit or that encodes the amino acid sequence of a proteinaceous biological unit, is divided into DNA fragments. A library of oligonucleotides, each comprising at least two of such fragments that are randomly ligated, is then created. Preferably, this library will contain oligonucleotides of fragment pairs in which each fragment is linked to each other fragment. If the biological unit is a protein or a complex of proteins, the oligonucleotides are inserted into an expression system and then expressed. If the biological unit is an RNA unit, the DNA is then transcribed to the corresponding RNA. The resultant is then screened for interaction with a ligand that interacts with a discontinuous epitope of the single biological unit. Those that are identified with such positive interaction are then produced and can serve to simulate the native discontinuous epitope.

Claims 144-151, 154-156, 159-165 and 168-170 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Huse in view of Stemmer. With respect to claim 144, the examiner states that Huse discloses a method of identifying and producing a peptide that interacts with the ligand that interacts with a discontinuous epitope of a single biological unit by providing a plurality of DNA fragments that appear in a DNA sequence encoding the single biological unit (i.e., antibody); creating a library of oligonucleotides comprising at least two randomly-ligated DNA fragments; inserting each of

said oligonucleotides into an expression system; expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with a ligand that interacts with a discontinuous epitope; and identifying the peptide and producing the identified peptide. The examiner concedes that, while Huse discloses applying the method to antibodies, it does not teach applying the method to a single gene. The examiner states that Stemmer teaches the use of a single gene at column 16, lines 15-18, that Example 8 shows application of the shuffling to a single antibody gene (it is believed that the examiner intended to refer to Example 7), and Example 9 applies the method to the β-lactamase gene. The examiner states that it would have been obvious to modify the method of Huse to apply the analysis to a single biological unit, such as a single gene, because Stemmer expressly teaches the desirability of using single genes. This rejection is respectfully traversed.

Stemmer differs from the basic concept of the present invention in the same manner as does Huse. Thus, Example 7 of Stemmer, which involves "shuffling" an antibody gene, is intended for the purpose of screening multiple antibody variations in order to select those that bind better to the original antigen. However, the positions within the single-chain antibody of each of the fragments are not changed during this shuffling. Note column 16, lines 41-43, where it states:

> Further, shuffling conserves the relative order, such that, for example, CDR1 will not be found in the position of CDR2.

The examiner relies heavily on column 16, lines 15-18, for the statement that the initial library "can be derived by any type of mutagenesis (including shuffling) of a single antibody gene." However, once a single antibody gene is subjected to mutagenesis, it is no longer a single biological unit. Each mutant is a separate biological unit. Thus, in Example 7, a critical step is synthetic mutagenization. See column 55, lines 6-14. It is the various mutations, for example, to CDR1, that are shuffled; but they are always placed in the position of CDR1. The fragments are not randomly ligated regardless of original position. Great care is taken to maintain the original position.

Claim 144 requires that one provide a plurality of DNA fragments, each of which appear in a DNA sequence that encodes a single biological unit. The examiner interprets this as being a single gene, although it should be noted that the preamble of claim 144 states that the single biological unit may be two or more proteins that interact to form a complex. The library consists of oligonucleotides from the plurality of DNA fragments, which fragments are randomly ligated. As there is only one fragment per position, it is impossible to ligate randomly if the positions are to be maintained as in Stemmer. If Stemmer truly started only with a single gene, there would be nothing to shuffle. It is respectfully submitted that the examiner is misinterpreting Stemmer in this regard as it is critical that the gene be mutagenized.

It is critical for the purpose of the present invention that the relative positions of the fragments be shuffled. The whole idea is to bring together fragments that are originally distant from one another in the linear sequence so as to mimic their positions in a discontinuous epitope.

Even if Stemmer were to teach shuffling the fragments of a single gene (which it does not), it is not understood how the examiner would propose to modify Huse in such a manner without completely destroying the entire purpose of Huse. Huse intends to generate a large combinatorial library of the immunoglobulin repertoire in phage lamda. Substituting a single gene for the library of Huse destroys Huse for its intended purpose. See *Ex parte Sternau*, 155 USPQ 733, 735 (Bd App 1967), where it states:

> However, there is nothing of Young and Haslacher that would teach the examiner's proposed combination or any reason for making it. In fact, the proposed combination would destroy the Young apparatus for its intended purpose. Thus, we will reverse the rejection on claims 44 and 45 for this reason.

The present invention is directed to a method of identifying and producing a peptide that interacts with a ligand that interacts with a discontinuous epitope of a single biological unit. Neither Huse nor Stemmer are directed to such a procedure, and the procedure of the present invention is not encompassed by anything done by Huse, Stemmer or any reasonable combination thereof. As claim 144 is patentable over prior art, all of the dependent claims must also be

patentable. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

submitted,

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